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AUTHOR Wolke, Dieter; And Others
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ABSTRACT

The study examined pre-, peri-, and neonatal factors in 271 British infants (weighing less than 1500 grams at birth), 188 of whom survived to 2 years. The study represented an attempt to define those factors which predict normal neurodevelopmental outcome in very low birth weight (VLBW) infants. Surviving infants were seen at 3, 6, 9, 12, and 24 months of age (corrected for gestational age) with follow-up examinations consisting of full physical, neurological, and developmental assessment, and further evaluation when appropriate. Major (such as cerebral palsy, severe hearing/visual disorders, severe developmental delay) and minor (such as epilepsy, partial hearing loss, moderate developmental delay) neurodevelopmental sequelae (NDS) were identified. Seventeen of the demographic, obstetric, and neonatal factors were significantly different between the 21 infants with major NDS and the 167 infants without major NDS. An additional nine infants showed minor neurodevelopmental problems. Three separate methods of multiple discriminant function analyses were performed. Best overall prediction was achieved by the direct entry method which classified 91.5% of infants correctly. The obstetric and neonatal factors which were good indicators of the overall degree of morbidity were hyponatraemia, the need for top-up transfusions, and pulmonary interstitial emphysema. (DB)

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PREDICTION OF NEURODEVELOPMENTAL SEQUELAE IN VLBW INFANTS[1]

Wolke, D., Brothwood, M., Gamsu, H. and Cooper, D.

King's College School of Medicine and Dentistry

Department of Child Health and Computing Unit

London

[1] The research was supported by a grant from the Wates Foundation and the Independent Order of Odd Fellows Manchester Unity Friendly Society. Correspondence should be addressed to Dieter Wolke, University of London, Institute of Child Health, Department of Child Psychiatry, The Hospitals for Sick Children, Great Ormond Street, London WC1N 3JH, England.

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The last decade has seen an impressive fall in the neonatal mortality of VLBW infants (Driscoll et al, 1982; Stewart et al, 1981; McCormick, 1985; Hack et al, 1979; Knobloch et al, 1982). This trend has been attributed to improved neonatal care (Thomson and Khot, 1985; Barson et al, 1984; Horwood et al, 1982; Reynolds and Stewart, 1979). However, neurodevelopmental sequelae (NDS) persist in a number of long term survivors. It is difficult to evaluate trends over time in the rate of these sequelae. Definitions of handicap that are used and the stringency of criteria for assessment vary in reported studies (Kitchen et al, 1982; Skouteli et al, 1985). Stewart et al (1981) have argued that the handicap rate is not increasing in spite of improved survival. Paneth et al (1981), Walker and Simpson (1982) and Stanley and Atkinson (1981) have pointed out that the decline in morbidity may not be keeping pace with the recent reduction in mortality thus resulting in a modest increase in the absolute number of survivors with impairment.

To ensure a good quality of life for VLBW infants it is important to identify those factors that predict normal developmental outcome (Skouteli et al, 1985; Low et al, 1985). Recent developmental and psychobiological models have emphasized that both reproductive and caretaking factors should be taken into account when predicting developmental outcome (Sameroff and Chandler, 1975; Horowitz, 1984). However, St James-Roberts (1986, in press) has hypothesized that while a responsive and facilitative caretaking environment may compensate for moderate reproductive casualty it may be unable to achieve full recovery if the damage to the infants intrinsic system exceeds his adaptive resources. Under these circumstances a main factor model

would be sufficient to predict developmental outcome.

Factors that have been associated with adverse developmental outcome in VLBW populations and that are of particular interest to neonatologists include extremely low birthweight, 5 minute Apgar scores (Skouteli et al, 1985; Knobloch et al, 1982), need for oxygen therapy, respiratory distress syndrome, recurrent apnoea (Knobloch et al, 1982), need for and duration of mechanical ventilation (Fitzhardinge et al, 1976; Ruiz et al, 1981; Saigal et al, 1982), neonatal seizures (Stewart et al, 1978; Nelson and Ellenberg, 1979), bronchopulmonary dysplasia (Ruiz et al, 1981), intra ventricular haemorrhage (Saigal et al, 1982), ventricular distension, cerebral atrophy or periventricular leucomalacia (Stewart, 1985a and b; Bozynsky et al, 1985; DeVries et al, 1985).

Several recent publications (Stewart, 1985a and b; Low et al, 1985; Siegel, 1982) have emphasized that the predictive value of peri- and neonatal factors should be evaluated in addition to the reporting of simple statistical differences between infants with and without NDS. Stewart (1985b) reported that neurodevelopmental outcome at 12 to 18 months can be accurately predicted in 65% to 83% of cases by neonatal brain ultra sound findings. Siegel (1982) correctly predicted developmental delay in cognitive functioning in VLBW children at three years using a simple risk score with 67.3% to 73.1% accuracy.

Furthermore, a number of researchers and clinicians have pointed out that most peri- and neonatal complications do not occur in isolation but are frequently associated or lead to other complications (Wolke and St James-Roberts, 1983; Minde et al, 1983). Both weighted or unweighted risk scoring systems (Werner et al, 1971; Littman and

Parmalee, 1978), optimality scoring systems (Prechtl, 1967) or daily weighted Morbidity Scales (Minde et al, 1983) have been proposed. However, with exception of Minde et al's morbidity scales, these indexes are not specifically designed for use with VLBW infants cared for in modern NICU's with new diagnostic and treatment facilities. They do not sufficiently discriminate between VLBW newborns and have poor predictive value (Littman and Parmalee, 1978).

The aim of this study is to examine a wide range of pre-, peri- and neonatal factors and to define those which predict normal neurodevelopmental outcome in VLBW infants.

Material and Methods

The study population consisted of 271 infants weighing 1500gms or less at birth who were admitted to King's College Hospital (KCH) Neonatal Intensive Care Unit over the three year period 1st January 1980 to 31st December 1982. 80.4% of infants were born to mothers in the KCH catchment area or to mothers who had been transferred for care antenatally. The other 19.6% of infants were born elsewhere and transferred to KCH for intensive care shortly after birth. The social class of fathers of study infants was predominantly IIIb (Registrar General's Classification of Occupations, 1980). Gestational age was calculated from mothers' last menstrual period and early antenatal ultrasound. Infants' weights were considered appropriate for gestational age if their birthweight was above the 10th percentile (Gairdner and Pearson, 1971).

Demographic, Obstetric and Neonatal Factors

Six demographic, 22 obstetric and 46 neonatal factors were recorded prospectively and are listed in Table 1.

(Insert Table 1 about here)

Clinical, Neurological and Developmental Assessment

Surviving infants were seen after discharge at 3, 6, 9, 12, and 24 months of age corrected for gestational age. The follow-up consisted of a full physical, neurological and developmental assessment by a developmental paediatrician not involved in neonatal care (M.B.). Infants who were suspected of having abnormal vision or hearing were referred for specialist ophthalmological or audiometric assessment. All infants with suspect or abnormal neurological examination received a repeat neurological assessment by a paediatric neurologist. These infants also had physiotherapy.

At one year of age, the Developmental Screening Inventory (DSI, Knobloch et al, 1966) was administered. This assessment like the Griffiths Scales (Griffiths, 1970) is adapted from the Gesell Developmental Scales (Gesell and Armatruda, 1947) and assesses the following areas: adaptive functioning, gross and fine motor abilities, verbal and personal social skills. At 2 years the Griffiths Scales were used to assess locomotor, personal-social, hearing and speech, eye and hand coordination and performance skills. Both assessments allow for general developmental quotients, and subquotients to be computed. Mothers were also interviewed concerning their infants progress, milestones, behaviour and family problems. All survivors were assessed in the first two years. Six infants (3.2%) were not available for assessment at one year at KCH. At two years, these six children were all assessed thus achieving a 99%

follow-up. One infant had moved abroad between one and two years and was reported to be normal. One child participated in a follow-up study of another London Teaching Hospital and full clinical, neurological and developmental reports were available for year one and two. Mean age for the one year and two year assessments (corrected for gestational age) were 12.3± 1.04 months (mean ± SD) and 24.3± 1.28 months respectively (for further details of the sample, see Brothwood, Wolke, Gamsu, Benson and Cooper, 1986).

Major neurodevelopmental sequelae (NDS) were defined according to Stewart (1985a). The major abnormalities identified by 24 months included cerebral palsy, sensorineural hearing loss, visual disorders such as delayed visual maturation, retinopathy of prematurity and overall developmental delay of sufficient severity to predict mental retardation (DQ corrected for prematurity of 70 or less). Minor neurodevelopmental sequelae were defined as follows: Epilepsy severe enough to necessitate continuous pharmacological treatment, partial hearing loss (no hearing aids required), hydrocephalus whether arrested or not in an otherwise normally developing child, abnormal muscle tone or moderate developmental delay (DQ between 71 and 85) (Driscoll et al, 1982; Ruiz et al, 1981; Orgill et al, 1982; Stewart, 1985a).

The data were analysed to evaluate those obstetric and neonatal factors which discriminate between infants who had NDS and those who did not.

The accuracy of predicting developmental outcome from obstetric and neonatal factors was evaluated by multiple discriminant function analysis (Hull and Nie, 1981).

Results

Of the total of 271 infants weighing 1500gm or less included in this study, 188 survived the first two years.

Comparison of perinatal factors between infants with normal and abnormal developmental outcome

Twenty-one of the 188 survivors had major NDS. Eight of these 21 infants with major neurodevelopmental disorder suffered multiple problems. Details of the survivors with major NDS are shown in Table 2. The degree of functional limitation caused by the neurodevelopmental impairment was rated using the classification described by Saigal et al (1982). Nine infants were judged to suffer major and minor dysfunction respectively and another three infants were judged to be mildly affected by their impairment.

(Insert Table 2 about here)

To reduce the number of independent variables to be entered in the Multiple Discriminant Function Analysis, Chi-square and t-test analysis were used to identify univariately discriminating factors.

Seventeen of the 74 demographic, obstetric and neonatal factors evaluated were significantly different between the 21 infants with major NDS and the 167 infants without major NDS.

In addition to the 21 infants with major NDS there were another 9 infants with minor neurodevelopmental problems (see Table 2, cases 22 to 30). The total of 30 infants with major or minor neurodevelopmental disorder (MMNDS) were compared to infants without neurodevelopmental problems. Twenty-three out of the 74 peri- and postnatal factors evaluated were significantly associated with neurodevelopmental sequelae. Details of these comparisons are reported elsewhere (Note 1).

Prediction of Developmental Sequelae

Multiple Discriminant Function analyses were used to examine the ability of a combination of obstetric and neonatal factors to detect those infants who would subsequently show developmental sequelae at two years. Three separate methods of entering the independent variables in the analysis were used. These three separate analyses methods were:

1. the direct-entry method which forces the whole set of variables into the analysis;
2. the stepwise method which enters variables one at a time until a predefined inclusion criteria is reached; and
3. a stepwise analysis whereby only three steps (3 variables) are allowed for entry.

The last stepwise analysis specifying a maximum of three steps was explored because it would be useful for the clinician if three key obstetric or neonatal factors would be sufficient to predict normal neurodevelopmental outcome. The earlier reported Chi-square and t-tests identified those single independent variables which discriminate between infants with and without major NDS. Thus, seventeen factors were entered in the multiple discriminant function analysis to determine a linear combination which best discriminates between the 21 infants with major NDS and those 167 without major NDS.

A second set of discriminant function analyses was performed to find the best multiple discrimination between all 30 infants with major and minor NDS (MMNDS) and those without neurodevelopmental sequelae. The earlier identified twenty-three factors which discriminated between these two groups using univariate tests were entered in the Discriminant Function analysis as independent

variables.

After the discriminant functions have been computed, the coefficients were used to predict group membership. Following the terminology of Scott (1978) and Siegel (1982), we called children who had developmental sequelae 'positive' and those who had no disorder 'negative'. The following classification scheme was used:

(a) true positives were children who were correctly predicted to have developmental disorder;

(b) false positives were children who were incorrectly predicted to have developmental sequelae;

(c) true negatives were children who were correctly predicted to be developmentally normal, and

(d) false negatives were children who were incorrectly predicted to be developmentally normal.

1) Major NDS (n=21) versus No Major NDS (n=167)

The obstetric and neonatal factors correctly predicted the developmental outcome in 87.8% to 90.4% of the cases depending on which analysis method was used.

Reasonable results in classifying the cases were reached by entering all 17 variables directly. More than 89.8% of cases were classified correctly (table 3, top row). There were only very few false positives (3.6%) and the overwhelming majority of true negatives were defined accurately. However, only 38.1% of infants with major NDS (true positives) were predicted correctly in spite of the discriminant function being highly significant ($X^2_{17} = 43.6$ $p < 0.001$). The factors with the highest standardized discriminant function coefficients ($d > .3$) were cervical incompetence during pregnancy

(.44), neonatal convulsions (.36), firstborn infant (.35), hyponatraemia (.33) and pulmonary interstitial emphysema (PIE, .30).

Tabachnick and Fidell (1983) have pointed out that discriminant function coefficients may be misleading and that loading matrices are important tools in interpreting discriminant functions. The loading matrix of correlations between predictor variables and discriminant function, seen in table 4 (left column) suggests that the primary variables in distinguishing between infants with major NDS and those without major NDS are hyponatraemia, the need for top-up transfusions, pulmonary interstitial emphysema (PIE), hypocalcaemia, lowest recorded haemoglobin and cervical incompetence. Only predictors with a loading of .35 or greater are shown in table 4. Smaller correlations are displayed between brackets and are included in table 4 (and table 6) for comparison purposes only. Seventy-one percent of infants with major NDS had experienced hyponatraemia whereas only 31% in the no major NDS group had had low sodium levels.

(Insert tables 3 and 4 about here)

The stepwise procedure correctly classified 90.4% of cases ($X^2_9 = 41.7$; $p < 0.001$). Again, there were very few false positives (2.4%). However, only 33.3% of infants with major NDS were correctly predicted by the 9 obstetric and neonatal factors accepted into the equation (table 3, middle row). Only the first four factors entered resulted in a significant change of V. These factors and their standardized discriminant coefficients were: hyponatraemia (.34), cervical incompetence (.47), PIE (.37) and neonatal convulsions (.36).

The loading matrix of correlations between predictor variables and discriminant functions was very similar to that reported for the direct discriminant function analysis (table 4, middle

column). However, three more neonatal factors showed correlations of .35 or greater with the discriminant function. These were recurrent apnoea, high ventilation pressures and neonatal convulsions.

Finally, the stepwise analysis limiting the number of predictors to three, also produced a significant discriminant function ($X^2_3 = 27.6$, $p < 0.001$). However, the classification analysis revealed that all but 4 of the 188 infants were predicted to develop normally (see table 3, bottom row). Only 1 of the 21 infants with major NDS was predicted correctly. The three factors entered in the equation and their standardized discriminant coefficients were cervical incompetence (.50), PIE (.54) and hyponatraemia (.59).

These three predictors had also the highest loadings on the discriminant function (table 4, third column). It is apparent that the loading matrix differs from the one's reported for the direct and stepwise analysis and is biased towards neonatal respiratory complications.

2) Major and Minor NDS (n=30) versus No NDS (n=158)

Best overall prediction and correct classification of infants was achieved by the direct entry method ($X^2_{23} = 79.0$, $p < 0.001$). One hundred and seventy-two of the 188 infants (91.5%) were classified correctly. There were 98.1% true negatives and 56.7% true positives (see table 5, top row). The obstetric and neonatal factors with highest standardized discriminant function coefficients ($d > .30$) were hydrocephalus neonatally (.62), cervical incompetence (.51), PIE (.41), the lack of long-term oxygen therapy (-.37) and hyponatraemia (.36). Inspection of the loading matrix revealed that hydrocephalus in the neonatal period, hyponatraemia and the need for top-up

transfusions were the primary factors in distinguishing between infants with and without MMNDS (table 6, first column).

(Insert tables 5 and 6 about here)

Ten variables were accepted in the equation using the stepwise method until the F-statistics indicated too low levels ($F < 1$) for further variables to be considered. These 10 factors significantly discriminated between MMNDS and Non-MMNDS infants ($X^2_{10} = 76.9$, $p < 0.001$). The classification analysis revealed that 89.4% of infants were correctly classified using the Discriminant Function. There were 98.1% true negatives and a substantially lower percentage of correctly predicted infants with MMNDS (true positives: 43.3%). The obstetric and neonatal factors with the highest discrimination function coefficients were hydrocephalus (.59), hyponatraemia (.37), cervical incompetence (.51), PIE (.38), first live birth (.29), frequent blood transfusions (.22) and lack of long-term oxygen therapy (.34). Hydrocephalus, hyponatraemia and the need for top-up transfusions were again contributing most to the discrimination between the two groups (table 6, second column).

Finally, the stepwise method limiting the number of predictors to be considered to three was also highly significant ($X^2_3 = 53.0$, $p < 0.001$). The three factors entered into the equation and their standardized discriminant function coefficients were: hydrocephalus (.74), hyponatraemia (.58) and cervical incompetence (.46). However, only 26.7% of the true positives were identified correctly when this discriminant function was used for classification purposes. Overall, 86.7% of infants were classified correctly and 98.1% of true negatives were predicted accurately (see table 5, bottom row). The loading matrix indicates that hydrocephalus and

hyponatraemia are the two most important predictors (table 6, third column).

DISCUSSION

The purpose of this study was to explore the relationship between obstetric and neonatal complications and the developmental status of VLBW infants at two years of age.

Twenty-one of the 188 VLBW survivors suffered major neurodevelopmental disorder. This 11.2% incidence of major NDS compares favourably with previous reports of developmental outcome in VLBW populations which used similar definitions of handicap (Saigal et al, 1982; Levene and Dubowitz, 1982; Kitchen et al, 1982). This finding also compares well with the results of a contemporaneous study by Stewart (1985b) whose definition of major NDS we adopted here. She found 11% of infants born between 1979 and 1982 of less than 33 weeks gestation to have major developmental disorder and a further 8% of infants had minor neurodevelopmental sequelae. By adopting a gestation rather than a birthweight criteria Stewart's (1985a and b) study included a number of infants above 1500g of birthweight. In our investigation a further nine infants (4.8%) had minor neurodevelopmental problems which were judged to cause mild limitations in everyday functioning. These figures can be tentatively interpreted as reflecting the results of improved neonatal intensive care.

However, we only used a 'wide-meshed net' in monitoring developmental outcome. Legacies of neonatal care other than neurodevelopmental including long-term respiratory problems (Levene and Dubowitz, 1982) have not been addressed in our study. Minde et al

(1983) and Field (1979) have also pointed to other short-term problems, in particular the lability and reduced responsiveness of the sick low birthweight infant in social interaction. Ideally, the identification of conditions affecting the quality of the child's life is achieved by long-term follow-up studies (Low et al, 1985). Assessment of school-age children should identify the full range of deficits, including learning disabilities and socioemotional and behavioural problems (Hunt, 1981; Bax, 1983) and also patterns of recovery. Unfortunately, these long-term follow-up studies can only provide rough guidelines because of the rapid changes in technology of life-support systems and medical care in neonatal intensive care units (Stewart et al, 1981; Korones, 1985). Long-term outcome of infants of different cohorts is likely to differ due to these changes.

Recent reports have indicated that peri- and neonatal complications are good predictors of short-term outcome (Low et al, 1985) and do predict subsequent motor and cognitive development in combination with assessments in infancy (Siegel, 1982). We found, indeed, a number of obstetric and postnatal factors, in particular, that predicted developmental outcome. Complications that best predict adverse outcome were hyponatraemia, hydrocephalus, the need for top-up transfusions and severe respiratory problems, in particular, the presence of PIE. Sensitivity and specificity of prediction (Haynes, 1981) was enhanced when both, major and minor NDS were considered and compared to infants without neurodevelopmental problems at 2 years of age.

The factors hyponatraemia, need for top-up transfusions and PIE seem to be good indicators of the overall degree of morbidity.

These three complications, although not reported here in detail, were found to have moderate correlations with other conditions including anaemia, recurrent apnoea, recurrent bradycardia, high pressure ventilation, neonatal convulsions, RDS, long-term oxygen therapy, IVH, hypophosphataemia and extremely low birthweight and gestation. Associations between these variables have been found in other studies. Greenough et al (1984) and Hart et al (1983) showed that PIE is a complication of RDS and high pressure ventilation, both of which we found to be associated with NDS. Neonatal anaemia and the need for replacement blood transfusions occur more often in the very small and sick infants. Blood sampling is likely to be more frequent in these babies. Later aneamia may be more pronounced if protein intake is insufficient (Ronnholm and Siimes, 1985). Urinary sodium loss increases with decreasing gestation (Rodriguez-Sorinao et al, 1983). Hyponatraemia also occurs in response to inappropriate arginine vasopressin secretion which is known to be associated with severe RDS, pneumothorax, asphyxia, IVH or sepsis (Rees et al, 1984; Shann and Germer, 1985). It has been suggested that arginine vasopressin release plays a role in the development and extension of IVH (Stark et al, 1982). Unfortunately, it may be difficult to decide clinically whether in an individual case hyponatraemia is due to inappropriate arginine vasopressin release or to sodium depletion.

Although birthweight and gestational age were associated with developmental outcome, these factors were not prime predictors of sequelae. This is in keeping with the concept that neurodevelopmental sequelae is not a result of prematurity per se, but rather the product of the fetal-newborn complications occurring in these children (Low et al, 1985).

Two other factors, hydrocephalus and cervical incompetence had no remarkable correlations with other complications but were associated with adverse neurodevelopmental outcome. Therefore, these two variables had high standardized discriminant coefficients. However, these coefficients may be misleading (Tabachnick and Fidell, 1983) as both these problems were rare in our sample. There were only 12 infants whose mothers had been diagnosed and treated for cervical incompetence; five of these suffered MMNDS. Seven infants developed hydrocephalus, six of these were handicapped at two years.

Overall accuracy and specificity of prediction on basis of the discriminant functions were good. However, normal neurodevelopmental outcome was predicted better than adverse outcome (Skouteli et al, 1985). We also found that three selected predictor variables, though statistically discriminating between NDS and healthy infants, are not sufficient in predicting outcome to be of clinical use. Both, direct entry and stepwise method provided moderate prediction of adverse outcome. In particular, more than 56% of infants with MMNDS, and more than 98% of healthy infants at 2 years were predicted by obstetric and neonatal factors only. This accuracy of detecting differential outcome in VLBW infants compares well to rates reported in the work by Stewart (1985a and b). Both, our results and those of Stewart (1985a and b) and Siegel (1982) have to be interpreted with some caution as they have not been crossvalidated in an independent sample.

Nevertheless, our findings lend support to the notion that a combination of life-threatening neonatal complications exceed the infants intrinsic (CNS-) systems resources for full recovery (St

James-Roberts, in press). This is particularly apparent when structural damage to the central nervous system such as cerebral palsy, sensorineural hearing loss, delayed visual maturation and retinopathy of prematurity are the outcome variables considered within an at risk group. Recovery from adverse neonatal conditions and their effects on more functional aspects of the intrinsic system, i.e. cognitive development are more likely to occur. It is reassuring that most of the infants with cerebral palsy or neurosensory problems had developmental quotients in the normal range, although somewhat lower than the mean because of sensorimotor limitations in these children. Assessments of visual recognition memory (Rose and Wallace, 1985) may be more appropriate for estimating cognitive abilities in these infants. While biological factors appear to be the principal variables affecting outcome during infancy (Low et al, 1985), socioeconomic characteristics and home environment are starting to exert their influence more and more after the child's first year of life (McCall, 1981; Gottfried, 1984). Longterm behavioural and cognitive development are best studied within a transactional framework (Sameroff and Chandler, 1975; Werner and Smith, 1982).

The prediction of even structural NDS is still far from perfect and may be enhanced by including more sophisticated regimes of brain investigation and diagnosis (Stewart, 1985b; DeVries et al, 1985) as well as repeated neurological assessments. However, some of these new and insufficiently evaluated tools may prove too expensive to buy, maintain and use by smaller NICUs.

Other factors, namely the physical and psychological environment may also have an effect on the at risk infants' development (Wolke, 1986; Gottfried and Gaiter, 1985; Als, in press).

Amount, type and timing of handling and noise pollution in the NICU have been associated with undesirable events like hypoxaemia, apnoea, changes in cerebral haemodynamics and increased intracranial pressure (Murdoch and Darlow, 1984; Gorski et al, 1983; Perlman and Volpe, 1983; Long et al, 1980). The latter have been suggested to play a role in the development and extension of intraventricular haemorrhage. Recently, Glass et al (1985) demonstrated in an intervention study that prolonged exposure to ambient nursery illumination results in significantly higher incidence of retinopathy of prematurity in extremely low birthweight infants, in particular. The subtle interactions of NICU environment and infant condition should also be considered when evaluating outcome in VLBW infants in future research (Wolke, 1986).

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Note 1

Wolke, D., Brothwood, M., Gamsu, H. and Cooper, D. (1986) Neonatal complications and the development of VLBW infants. (submitted for publication)

TABLE 1 : LIST OF PROPECTIVELY RECORDED DEMOGRAPHIC, PERI- AND NEONATAL VARIABLES

Demographic

1. Maternal age
2. Civil status
3. Social class (based on father's occupation)
4. Social class (based on mother's last occupation)
5. Mother's racial origin (caucasian)
6. Father's racial origin (caucasian)

Obstetric

7. Significant maternal medical history (psychiatric, physical, drug addiction)
8. Previous live births
9. Previous still births
10. Previous neonatal deaths
11. Previous spontaneous abortions or miscarriages
12. Maternal smoking
13. Multiple pregnancy
14. Antepartum haemorrhage (APH)
15. Pregnancy induced hypertension (blood pressure>140/90 and significant albuminuria) (PET)
16. Hypertension (blood pressure >140/90)
17. Premature rupture of membranes (PROM > 24 hours)
18. Premature labour
19. Admission in advanced labour
20. Cervical incompetence
21. Uninary tract infection
22. Maternal diabetes (diet and/or insulin)
23. Insufficient antenatal care (booked >20 weeks or no ANC)
24. Intra uterine growth retardation (IUGR; <10th percentile)
25. Breech presentation
26. Mode of delivery (caesarean section)
27. Fetal distress
28. Place of birth (outborn)

Neonatal

29. Infant's sex
30. Birthweight
31. Gestational age
32. Apgar score at 1 minute
33. Apgar score at 5 minutes
34. Intubation at birth
35. Recurrent apnoea (5 episodes >20 seconds)
36. Recurrent bradycardia (5 episodes of heart rate <100 per min)
37. Respiratory distress syndrome (RDS)
38. Transient tachypnoea (TTN)
39. Pulmonary interstitial emphysema (PIE)
40. Pneumothorax
41. Pneumonia
42. Aspiration (milk, meconium, blood)
43. Bronchopulmonary dysplasia (BPD:persisbent pathological changes)
44. Intra ventricular haemorrhage (IVH)
45. Hydrocephalus (OFC >2 S.D.)
46. Convulsions
47. Patent ductus arteriosus (PDA)
48. Necrotising enterocolitis (NEC)
49. Septicaemia (confirmed by blood culture)
50. Meningitis (confirmed by CSF culture)
51. Congenital malformations
52. Ventilatory support (IPPV or CPAP)
53. Duration of ventilatory support (days)
54. Oxygen therapy
55. Prolonged oxygen therapy (>20 days)
56. Maximum F_iO_2
57. Hypoglycaemia (Dextrostix <25 mg% or blood sugar <1.4 mmol/l)
58. Maximum serum bilirubin
59. Phototherapy
60. Hyponatraemia (<1.25 mmol/l)
61. Hypocalcaemia (<1.75 mmol/l)
62. Lowest haemoglobin (g/dl)
63. Alkaline phosphatase (>400 IU/l)
64. Hypophosphataemia (1.3 mmol/l
65. Rickets (radiological evidence)
66. Hypothermia (<35.0°C)
67. Umbilical arterial catheter inserted (UAC)
68. Replacement blood transfusions
69. Dextrose infusion
70. Intralipid infusion
71. Amino-acid infusion
72. Age regaining birthweight (days)
73. Lowest weight as percentage of birthweight
74. Parental bonding (concern)

TABLE 2: SURVIVORS WITH DEVELOPMENTAL SEQUELAE

1. Major Neurodevelopmental Disorder (n= 21)

Case	Gestation (weeks)	Birth weight (gm)	Sex	Place of Birth	Major Neuro-developmental disorder	General DQ (corrected) at age 24 months	Functional handicap
1	32	1170	M	OB	-Right hemiplegia -Arrested hydrocephalus -Intellectually subnormal	52	Major
2	28	1250	M	KCH	-Sensorineural hearing loss	101	Moderate
3	28	1050	M	OB	-Sensorineural hearing loss	95	Moderate
4	28	1170	M	IUT	-Spastic diplegia	102	Mild
5	31	1000	F	OB	-Spastic quadriplegia	93	Major
6	28	1400	F	OB	-Spastic quadriplegia -Sensorineural hearing loss -Arrested hydrocephalus	99	Major
7	26	820	M	KCH	-Retro-orbital haemangioma right eye-partial sight	101	Mild
8	33	1410	F	KCH	-Spastic quadriplegia -Intellectually subnormal	58	Moderate
9	30	1000	F	OB	-Sensorineural hearing loss	122	Moderate
10	29	820	F	IUT	-Spastic quadriplegia -Delayed visual maturation -Intellectually subnormal	24	Major

Case	Gestation (weeks)	Birth weight (gm)	Sex	Place of Birth	Major Neuro-developmental disorder	General DQ (corrected) at age 24 months	Functional handicap
11	26	770	F	IUT	-Right hemiplegia -Refraction error (squint) -Partial hearing loss (no aids)	74	Moderate
12	32	1410	M	KCH	-Developmental delay -Intellectually subnormal	63	Major
13	32	1220	M	OB	-Spastic quadriplegia	95	Major
14	26	820	M	OB	-Sensorineural hearing loss	103	Moderate
15	29	1180	M	OB	-Sensorineural hearing loss	90	Moderate
16	29	880	M	IUT	-Spastic quadriplegia -Intellectually subnormal	49	Major
17	30	1410	M	KCH	-Spastic diplegia	106	Mild
18	31	1120	M	IUT	-Spastic diplegia	90	Major
19	29	1440	F	IUT	-Spastic quadriplegia	79	Moderate
20	26	1030	M	IUT	-Spastic diplegia -Retinopathy of prematurity -Partial hearing loss -Arrested hydrocephalus -Intellectually subnormal	30	Major
21	26	940	F	IUT	-Sensironeural hearing loss -Delayed visual maturation -Developmental delay	65	Moderate

2. Minor Neuro-Developmental Sequelae (n=9)

Case	Gestation (weeks)	Birth weight (gm)	Sex	Place of Birth	Major Neuro-developmental disorder	General DQ (corrected) at age 24 months	Functional handicap
22	30	1240	M	OB	-Abnormal muscle tone (floppy) -Hydrocephalus with ventriculoperitoneal shunt	76	Mild
23	32	700	F	OB	-Abnormal muscle tone -Hydrocephalus with ventriculoperitoneal shunt	116	Mild
24	28	960	M	KCH	-Abnormal muscle tone	87	Mild
25	30	1420	M	OB	-Developmental delay -Squint	77	Moderate
26	30	1130	M	IUT	-Developmental delay -Squint -Hyperactive	82	N/A
27	30	1000	M	IUT	-Moderate conductive hearing loss -Arrested hydrocephalus	89	Mild
28	31	800	M	OB	-Congenital hydrocephalus arrested -Klinefelter syndrome	75	Mild
29	27	820	M	KCH	-Developmental delay -Acquired equinovarus deformity -Hyperactive	77	N/A
30	29	1160	F	IUT	-Developmental delay	84	Mild

N/A: These infants are not classifiable using Saigal et al (1982) classification system
KCH: King's College Hospital
IUT: In-uterine transferral
OB: Outborn

TABLE 3 - RESULTS OF THE CLASSIFICATION ANALYSIS USING THE DIFFERENT DISCRIMINANT FUNCTIONS

MAJOR NDS VERSUS NO MAJOR NDS

True Negatives	True Positives	False Negatives	False Positives	% Correct Prediction
		I Direct Entry Method		
161	8	13	6	89.9
		II Stepwise Method		
163	7	14	4	90.4
		III Stepwise Method (3 steps only)		
167	1	20	3	87.8

TABLE 4: RESULTS OF DISCRIMINANT FUNCTION ANALYSES (MAJOR NDS VERSUS NO MAJOR NDS)

Predictor Variables	Correlations of Predictor Variables with Discriminant Function (>.35)			Univariate F(1,186)
	Direct	Stepwise	Stepwise (3 steps only)	
Hyponatraemia	.52	.54	.68	14.1***
Top-up transfusions	.47	.41	.35	11.6***
PIE	.44	.46	.58	10.2**
Hypocalcaemia	.44	.45	(.24)	9.8**
Lowest haemoglobin	-.41	-.43	(.28)	8.9**
Cervical incompetence	.35	.37	.47	6.5*
Recurrent apnoea	(.28)	.36	.39	4.0*
High ventilation pressure	(.34)	.35	(.29)	6.0*
Neonatal convulsions	(.33)	.35	(.02)	6.0*
RDS	(.33)	(.32)	.43	5.7*
Oxygen therapy	(.29)	(.30)	.38	4.4*
Canonical R	.47	.45	.37	
Eigenvalue	.279	.258	.162	

*** $p < 0.001$
** $p < 0.01$
* $p < 0.05$

TABLE 5 - RESULTS OF THE CLASSIFICATION ANALYSIS USING THE DIFFERENT DISCRIMINANT FUNCTIONS
MMNDS VERSUS NO NDS

True Negatives	True Positives	False Negatives	False Positives	% Correct Prediction
		I Direct Entry Method		
153	17	13	5	91.5
		II Stepwise Method		
155	13	17	3	89.4
		III Stepwise Method (3 steps only)		
155	8	22	3	86.7

TABLE 6: RESULTS OF DISCRIMINANT FUNCTION ANALYSES

(MMNDS VERSUS NO NDS)

Predictor Variables	Correlations of Predictor Variables with Discriminant Function (> .35)			Univariate F(1,186)
	Direct	Stepwise	Stepwise (3 steps only)	
Hydrocephalus	.53	.56	.70	30.4***
Hyponatraemia	.44	.45	.57	20.2***
Top-up transfusions	.42	.44	(.24)	19.2***
Oxygen therapy	(.31)	.37	(.23)	9.9**
Recurrent apnoea	(.28)	.36	(.28)	6.6**
PIE	(.34)	.35	(.02)	12.2***
Canonical R	.60	.59	.50	
Eigenvalue	.572	.529	.333	

*** $p < 0.001$
** $p < 0.01$
* $p < 0.05$